Pharmacokinetics of linezolid during extracorporeal membrane oxygenation

Pharmacokinetics Of Linezolid

During Extracorporeal Membrane Oxygenation

Sir,

The extracorporeal membrane oxygenation (ECMO) is increasingly used in the critical setting for patients with respiratory failure and there is a growing body of knowledge describing the associated variations in plasma concentrations of drugs, including antibiotics, due to drug adsorption on the different components of the ECMO circuit. Currently, a multicentre study is ongoing to confirm if the standard antibiotic dosing in adult patients may still be considered appropriate [1]. Linezolid (LNZ) is extensively used in patients with pneumonia in critical care because of its strong activity against *Staphylococcus aureus* and its high pulmonary penetration, but there are no data on LNZ pharmacokinetics during ECMO [2]. Here we report the main pharmacokinetic parameters in three critically ill patients on ECMO treated with LNZ.

Patient 1 was a 61-year-old man, with a body mass index (BMI) of 24, who underwent lung transplantation because of chronic obstructive pulmonary disease and was treated with LNZ for pneumonia caused by meticillin-resistant *S. aureus* (MRSA) with a LNZ minimum inhibitory concentration (MIC) of 1 mg/L. Patient 2 was a 40-year-old woman (BMI = 18) with cystic fibrosis (CF) who was on the transplant list, empirically treated with LNZ and previously colonised by MRSA. Patient 3 was a 32-year-old woman (BMI = 31) with severe pneumonia caused by influenza H1N1 and pulmonary bacterial superinfection by meticillin-susceptible *S. aureus* (LNZ MIC

= 4 mg/L) isolated from bronchoalveolar lavage, previously treated with oxacillin that was stopped because of jaundice.

Plasmatic concentrations of LNZ were studied during ECMO, after informed consent was signed, at steady-state with the standard dosage of 600 mg every 12 h intravenously by 1-h infusion. The area under the curve (AUC) of daily ($AUC_{0–24}$) plasma concentrations of LNZ was calculated with blood samples collected before (time 0) and 1, 2.5, 4, 6 and 8 h after the intravenous administration. Minimum plasma concentration (C_{min}) is defined as the concentration before the administration and the maximum plasma concentration (C_{max}) is defined as the concentration at the end of the infusion. LNZ was determined in plasma by ultra performance liquid chromatography-photodiode array (UPLC-PDA) method. Pharmacokinetic data were studied using Kinetica software (Thermo Scientific, Waltham, MA) and $AUC_{0–24}$ was calculated as $AUC_{0–24} = 2 \times AUC_{0–12}$ [3]. In Table 1 the main LNZ pharmacokinetic parameters are reported, such as C_{max}, C_{min}, $AUC_{0–24}$, half-life ($t_{1/2}$), clearance (CL), time above the MIC (t > MIC) and volume of distribution (V_d); we also reported in Table 1 the LNZ pharmacokinetic parameters calculated with *S. aureus* MICs corresponding to 1, 2 and 4 mg/L for Patients 1, 2 and 3, respectively.

These results show that the calculated pharmacokinetic parameters of LNZ during ECMO are satisfactory when the MRSA MIC is ≤1 mg/L, with AUC_{0-24}/MIC ratio ≥80 in all patients [3, 4]. Only patient 3 did not display a full 24-hour plasma concentration above the MIC = 1 mg/L, with t > MIC corresponding to 66% of the

dosing interval. The rate of achievement of pharmacological parameters decreases for all patients with MIC values > 1 mg/L, as detailed in Table 1, for both AUC_{0-24}/MIC ratios and *t* > MIC.

This is the first report of LNZ plasma concentrations in patients treated with ECMO, where we also included calculated data for different MICs to provide a reference for future patients. According to our data, even if limited, pharmacokinetic targets are not achieved with standard dosage of LNZ when the MRSA MIC is >1 mg/L. Notwithstanding the limited sample size and heterogeneity of patients, including lung transplant, CF and high BMI, we conclude that plasma pharmacodynamic targets are easily achieved only when the *S. aureus* MIC is ≤1 mg/L. According to our results, patients infected by *S. aureus* with MICs > 1 mg/L on ECMO should be considered, pending future confirmation, at considerable risk of inadequate pharmacokinetic coverage. Prolonged or continuous infusion of LNZ might be needed in critically ill patients to increase AUC_{0-24}/MIC ratios or t > MIC, as well as increased dosage or combination therapy.

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Table 1.

Pharmacokinetic parameters of linezolid for patients 1, 2 and 3, and calculated data for *Staphylococcus aureus* minimum inhibitory concentrations (MICs) of 1, 2 and 4 mg/L.

	Patient 1	Patient 2	Patient 3
Pharmacokinetic parameters			
C_{max} (mg/L)	15.67	18.51	15.61
C_{min} (mg/L)	4.25	0.47	0.43
$AUC_{0–24}$ (mg h/L)	212.58	165.65	100.59
CL (L/h)	5.65	7.24	13.35
V_d (L)	49.7	17.6	46.77
$t_{1/2}$ (h)	6.10	1.68	2.20
Calculated data			
$AUC_{0–24}$ /MIC (MIC = 1)	212.58	165.65	100.58
$AUC_{0–24}$ /MIC (MIC = 2)	106.29	82.83	50.30
$AUC_{0–24}$ /MIC (MIC = 4)	53.14	41.41	25.15
t>MIC (MIC = 1) (% over 12 h)	100	100	66
t>MIC (MIC = 2) (% over 12 h)	100	75	41
t>MIC (MIC = 4) (% over 12 h)	100	58.3	30

C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; $AUC_{0–24}$: area under the curve of plasma daily concentrations; CL, clearance; V_d, volume of distribution; $t_{1/2}$, half-life; *t*>MIC, time of plasma concentrations above the MIC.